Immune and Inflammatory Determinants Underlying Alzheimer's Disease Pathology.

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Funding Grants: An exosome-based translational strategy to mitigate Alzheimer's disease neuropathology

Public Summary:
This study uses human and Alzheimer Disease (AD) human patients and rodent models to show that humans and rodents that exhibit only mild AD dementia also have a weaker immune response. On the other hand humans and rodents that exhibit severe dementia also have a very strong immune response. These outcomes also correlated with inflammation in the blood and in the brain where more severe AD exhibits high levels of inflammation that than damage the brain.

Scientific Abstract:
This study examines the link between peripheral immune changes in perpetuation of the Alzheimer's disease (AD) neuropathology and cognitive deficits. Our research design using human AD patients and rodent model is supported by past evidence from genomic studies. We observed an active immune response against Abeta as indicated by the increased Abeta specific IgG antibody in the serum of AD and patients with mild cognitive impairments as compared to healthy controls. A similar increase in IgG and decrease in IgM antibody against Abeta was also confirmed in the 5xFAD mouse model of AD. More importantly, we observed a negative correlation between reduced IgM levels and cognitive dysfunction that manifested as impaired memory consolidation. Strong peripheral immune activation was supported by increased activation of microglia in the brain and macrophages in the spleen of AD mice compared to wild type control littermates. Furthermore, inflammatory cytokine IL-21 that is involved in antibody class switching was elevated in the plasma of AD patients and correlated positively with the IgG antibody levels. Concurrently, an increase in IL-21 and IL-17 was observed in spleen cells from AD mice. Further investigation revealed that proportions of T follicular helper (Tfh) cells that secrete IL-21 are increased in the spleen of AD mice. In contrast to Tfh, the frequency of B1 cells that produce IgM antibodies was reduced in AD mice. Altogether, these data indicate that in AD the immune tolerance to Abeta is compromised leading to chronic immune/inflammatory responses against Abeta that are detrimental and cause neuropathology. Graphical Abstract Healthy subjects are tolerant to Abeta and usually react weakly to it resulting the in the production of IgM class of antibodies that are efficient at clearing up self-antigens such as Abeta without causing inflammation. In contrast, Alzheimer's disease patients mount a strong immune response against Abeta probably in an effort to clear up excessive Abeta. There is enhanced production of inflammatory cytokines such as IL-21 as well as an increase in Tfh cells that cause antibody class switching form IgM to IgG. The strong immune response is inefficient at clearing up Abeta and instead exacerbates inflammation that causes AD neuropathology and cognitive dysfunction.